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A Comprehensive Review Of Multi-Omics, Network Pharmacology, And Artificial Intelligence Approaches To Heart Failure

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ABSTRACT

Heart failure continues to be a pandemic of the twenty-first century, a major contributor to which are chronic diseases and the increasing number of elderly people. The transition from the outdated "dropsy" to the modern neurohormonal theory of the illness is reviewed. Beta-blockers, MRAs, ARNIs, and SGLT2 inhibitors are the core "scaffold" of medicines that have improved nearly all patient outcomes, which is why treatment has revolutionized itself. However, since genetics recognizes the genetic variability of heart failure situations, it holds the key to the sector's future. The goal of this effort is to identify illness endotypes for customized therapeutic care, driven by bioinformatics and multi-omics data. On top of that, the scientists are keen on implementing the same technology and in silico approaches to explore phytocomplexes with multitarget activity. AI and machine learning have dramatically transformed the pharmaceutical industry, disease prediction, and diagnostic procedures. This paper elucidates the evolution of heart failure management from an indiscriminate, reactive model to a tailored, systems-based, preventive paradigm.

ABBREVIATIONS:
HF: Heart Failure
HFrEF: HF with reduced Ejection Fraction
HFpEF: HF with preserved Ejection Fraction
SGLT2i: Sodium-Glucose Cotransporter-2 Inhibitor
ARNI: Angiotensin Receptor-Neprilysin Inhibitor
MRA: Mineralocorticoid Receptor Antagonist
AI: Artificial Intelligence
ML: Machine Learning
scRNA-seq: Single-Cell RNA sequencing
RAAS: Renin-Angiotensin-Aldosterone System

INTRODUCTION

Heart failure (HF) is a complicated medical situation that still ends up on the list of top causes of death and incapacity all over the globe. Furthermore, it is a major and escalating problem in public health (Khan et al., 2024; Savarese et al., 2023). Its complicated progression is a result of multiple aetiologies, most commonly of coronary artery disease, and it is maintained by a cycle of mechanical stress and neurohumoral activation that produces non-beneficial

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cardiac remodeling (Katz, 1992; Mann, 2002). Conceptually recently, the history of heart failure (HF) has been changed from an ancient era to a clinically complex disease of present day (Cohn, 2004; van den Bogaard & Veenstra, 2011). Some of the earliest indications of what has been known as HF in the present day can be found in ancient medical books. To illustrate, both Egyptian papyri and traditional Chinese medical literature referred to a new thing called "dropsy," or generalized oedema (van den Bogaard & Veenstra, 2011). While the ailment was considered a failure of the body's internal vital processes, these initial concepts saw the symptoms as being caused by an energy or humoral imbalance rather than by a specific organ malfunction.

The scientific revolution was among the most prominent moments. It takes an understanding of the circulatory system to recognize the heart as a pump, and that system was introduced by William Harvey's groundbreaking 17th-century work De Motu Cordis (van den Bogaard & Veenstra, 2011). In fact, the science did not yet give a full picture of HF only from the mechanical side. Only towards the 18th century when William Withering and other people made their contributions, most notably their pharmacological aspect (William Withering and the digitalis, 2008). The empirical study of Withering on the administration of foxglove, a digitalis source, for the treatment of dropsy evidenced a direct linkage between a certain chemical and symptom relief, thus, a substantial move towards pharmacological therapy for dropsy was achieved (William Withering and the digitalis, 2008).

The simple "pump failure" idea was no longer sufficient in the 20th century. Experimental data acknowledged that HF was a systemic problem with neurohormonal systems activation rather than a mechanical issue alone (Cohn, 2004; Katz, 1992). This chronicle of "neurohormonal" period introduced the roles of hormones, the sympathetic nervous system, and the renin-angiotensin-aldosterone system (RAAS) that are involved in the pathogenesis of the disease (Katz, 1992). This new concept cleared the way for modern drugs like beta-blockers and ACE inhibitors and at the same time explained the ineffectiveness of the use of inotropes such as digitalis that had been the only treatment option before (Cohn, 2004; Pitt et al., 1999). Also, from the middle of the 20th century, the Framingham Heart Study has been a very significant contributor in shifting the view of the HF from a sole, unambiguous diagnosis to a clinical descriptor with risk factors that can be identified and a natural course of progression (Ho et al., 1993). The patient treatment that is more proactive and preventive was not only early, but also firmly based on its long-term, epidemiological statistics (Ho et al., 1993).

Experiments on the subject of medical science alongside the usage of the latest methods in the treatment of heart failure (HF) have led to the conclusion that the research corridors of HF are non-linear. Therefore, they are relationships that, to a certain extent, can either restrict the impact of the previous failures and successes or, equally, extend it (Cohn, 2004; Packer, 2005). The chief consequence of this recurrent historical actuality is that the dominant medical paradigms, which are often considered the most valid ones, turn out to be inadequate most of the time, thus resulting in a wider understanding as shown in figure 1.

One of the most striking examples of such conceptual advancement is the transition from the simple "pump failure" theory to the "neurohormonal" hypothesis (Katz, 1992). The primary idea around heart failure, which lasted for several years, was that it ought to be seen as a mechanical fault, the heart being unable to push the blood through properly. treatments that involved using substances like digitalis to boost the heart's contractions (William Withering and the digitalis, 2008). Although this approach relieved some of the patients' symptoms, it did not stop the disease development. The "neurohormonal" period history is characterized by a major revolution of the paradigm era in the middle of the last century (Katz, 1992). The compensatory mechanisms that the body activates, the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS), for example, were found to be the reason for the progression of the disorder rather than the solution (Katz, 1992; Triposkiadis et al., 2023). As a result of such a discovery, researchers were able to create strong drugs, such as ACE inhibitors, beta-blockers, and mineralocorticoid receptor antagonists that target these pathways and significantly changed the outcomes of the patients (Heidenreich et al., 2022; Pitt et al., 1999).

The "multi-omics" and "personalized" models are leading the way and are expected to have a major influence on the field once again (He et al., 2023; Shah & Vaduganathan, 2016). The "neurohormonal" model, which had been the mainstay, is still regarded as a simplification by those who recognize the manifold individual differences in therapeutic response and patient development. The "multi-omics" approach integrates data from various levels of biology, such as transcriptomics, proteomics, metabolomics, and genomes, for a single biological system (He et al., 2023; Red-Heart-Failure-Group, 2017). Understanding the DNA, protein expression, and metabolic profile of each patient allows finding new subtypes of diseases, along with the associated risk factors (Arnett et al., 2020; He et al., 2023). With the advent of drugs that are tailored to match the specific biological fingerprint of each patient, the era of fully personalized medicine is set to follow and the approach of "one-size-fits-all" treatment will be left behind (Shah & Vaduganathan, 2016).

The history of medicine is another example of discovery being a strong cyclical process. Often ideas that were forgotten or had been left incomplete are being rediscovered and enhanced with the help of new technologies. The inflammation theme provides a perfect example (Mann, 2002). Dropsy and swelling were terms that went hand in hand in the ancient medical world, most likely since the two were always found together (van den Bogaard & Veenstra, 2011). It turned out that the practical and later neurohormonal models had

replaced the old concept completely. By using extremely sensitive methods of molecular biology to examine the issue of chronic low-grade inflammation in the development of heart failure, scientists have rekindled interest in the matter (Mann, 2002). The uncovering of the inflammatory routes in the heart and blood vessels is allowing the development of new directions for research and the design of anti-inflammatory medicines targeted to heart failure (Mann, 2002).

The current situation is dominated by two revolutions going on at the same time: the first one of technology, driven by data science developments, and the second one of pharmacy, characterized by drug classes that save lives and are the main targets for neurohormonal systems (Heidenreich et al., 2022; Packer et al., 2020). There are still many problems despite these improvements, for example, the marked heterogeneity of the disease, the HFpEF phenotype that has been difficult to treat and the disparities of healthcare access in different parts of the world (Lopez et al., 2017; Shah & Vaduganathan, 2010; Ziaeian & Fonarow, 2020). This review is committed to giving a big picture of heart failure (HF) by detailing the pathophysiology and global impact of HF, giving an account of its medical background, and acknowledging the ongoing pharmaceutical revolution. After that, it moves on to describe the novel bioinformatics technologies that are reshaping the area of accurate, personalised HF treatment, for example, artificial intelligence, network pharmacology for phytochemicals, and multi-omics integration (figure 2) (He et al., 2023; Hopkins, 2007; Rumsfeld & Curtis, 2019; Zhang et al., 2018).

International Health Crisis

The occurrence of congestive heart failure (HF) and YLD related to HF have grown substantially since 1990, as the Global Burden of Disease Study (GBD) 2021 data shows (Ran et al., 2025). The global number of people affected by HF has doubled from 25.4 million (95% UI 22.3-29.2) in 1990 to about 55.5 million [95% UI 49.0-63.8] in 2021. The doubling of the prevalence is an indicator of the increasing impact of heart failure on global health. The huge effect of this is also noticeable in the age-standardized prevalence rate that came to 676.7 per 100,000 population (95% UI 598.7–776.8). As per gender-specific analysis, males were more affected compared to females. The prevalence rate for males was 760.8 per 100,000 (95% UI 673.2–874.7) whereas for females, it was 604.0 per 100,000 (95% UI 535.0–692.3) (Ran et al., 2025). Furthermore, HF rates have also gone up markedly during the same period. The prevalence-related YLDs have gone up by 5.5% (95% CI 2.7–8.5), and the disability-associated YLDs have risen by 5.9% (95% CI 2.9–9.0), thus indicating the increased functional and socioeconomic impact of HF (Ran et al., 2025).

Ischemic Heart disease has been identified as the main cause of heart failure by an etiological study analyzing GBD 2021 data with an age-standardized prevalence rate of 228.3 per 100,000 (95% UI 118.2-279.6) (Ran et al., 2025). The following highest rates are 148.3 per 100,000 (95% UI 117.3-186.3) for hypertensive heart disease and 62.0 per 100,000 (95% UI 51.2-73.2) for cardiomyopathy or myocarditis. When comparing across the sociodemographic index (SDI) spectrum significant differences become clear: high-SDI nations have been characterized by steady trends, which is a sign of progress in long-term disease management and early identification, despite their overall prevalence being higher (Khan et al., 2024; Ran et al., 2025). Low-SDI countries, in contrast, that were first marked by relatively lower prevalence, have raised their age-standardized HF prevalence and YLD rates. One of the reasons for this disturbing trend is the rise in lifespan, the scarcity of medical care, and the increase of risk factors that are mainly obesity, diabetes, and hypertension (Ziaeian & Fonarow, 2020).

The situation that HF is becoming a major challenge that progresses rapidly and is expected to become more severe in the future decades and is going to affect every area of the world, is acknowledged by many authors (Packer, 2005; Savarese et al., 2023). Moreover, the risk of developing HF during a lifetime has gone up to 24%, implying that roughly one in four persons will suffer from this condition at some point in their lives (Ho et al., 1993). In spite of the occurrence of heart failure (HF) that tends to be getting fixed or even going down in some wealthy countries, mortality rates, especially those of younger populations, have been climbing in a variety of regions (Shah & Vaduganathan, 2015). The gradual spread of the illness all over the world is showing that it is a changeable and persistent source of danger, so the requirement for strong public health measures is still quite obvious.

Many epidemiological and demographic changes have been the primary drivers of the increased occurrence of heart failure. Among the leading contributory factors is the ageing of the global population because the risk of heart failure increases dramatically with age (Khan et al., 2024; Savarese et al., 2023). The survival rate from other cardiac problems has improved, and more individuals in wealthy countries have reached the age at which they are prone to heart failure. Consequently, the number of elderly people with multiple health problems is growing. Besides that, the increase of heart failure cases in all age groups is being linked with the rising global prevalence of major risk factors, such as diabetes and obesity (Kenchaiah et al., 2002). The research that the proportion of deaths from heart failure due to obesity has almost tripled in the last two decades, and the death rate from obesity-related HF has increased significantly among the youth shows that (Kenchaiah et al., 2002). The combined effect of these diseases is a vicious cycle where each risk factor worsens the others leading to the accelerating of heart failure progression.

Heart failure has an enormous financial burden that is deteriorating. In some areas of the globe, heart failure is

the chief cause of hospital admissions among the elderly. Moreover, this represents a major part of the healthcare budget in affluent countries (Cook et al., 2014). The authors of the study say that HF will be a burden on the world's economy amounting to $284 billion by 2021 (Cook et al., 2014). The money referred to in the text is not only a very large amount of direct medical expenses like hospital stays but also a substantial amount of indirect costs like lost productivity caused by disability and premature death. The amounts paid by individuals for a single patient are congestive heart failure (CHF) can be very large, especially for low-income families (Cook et al., 2014; Ziaeian & Fonarow, 2020).

The occurrence of heart failure (HF) varies significantly between wealthy and low-income countries, not only locally but also worldwide (Khan et al., 2024; Ziaeian & Fonarow, 2020). Most of the credit for this turnaround in high-income countries (HICs) with the trend from heart failure (HF) going downward or being stopped should be given to the treatment of risk factors through well-managed hypertension and the use of public health measures that have proven to be effective (Heidenreich et al., 2022; Yancy et al., 2013). Along with the stabilizing trend in HICs, the overall occurrence of HF is still high because the survival rate after the first cardiac incident has risen substantially. Their health systems, by providing state-of-the-art surgical procedures, medication therapies, and diagnostics, are also capable of achieving outcomes that are lower than mortality rates (Heidenreich et al., 2022).

In contrast, the occurrence and range of heart failure in low-middle-income countries are going up very fast (Khan et al., 2024; Ziaeian & Fonarow, 2020). These factors reflect the changes in the places that the people live, the increasing number of people, and the rising trend of non-communicable diseases that exceed those of infection diseases in the epidemiological transition. Due to the occurrence of risk factors for HF like obesity, diabetes mellitus, and hypertension, the number of HF patients in these areas has increased significantly (Kenchaiah et al., 2002; Ziaeian & Fonarow, 2020). There are large problems with the healthcare systems in many LMICs. The listed reasons include poor compliance with proposed treatment options, the lack of healthcare staff, and limited access to affordable diagnostic technologies (Huffman & Prabhakaran, 2010; Ziaeian & Fonarow, 2020). Such structural barriers lead to a delayed diagnosis, substandard treatment, increased hospitalization, and a considerably higher mortality rate as compared to HICs (Sathish et al., 2024). The money needed to take care of the rising number of heart failure patients in areas lacking sufficient medical resources is among the major hindrances to sustainable development and healthcare equity, the authors stipulate (Figure 3) (Cook et al., 2014; Ziaeian & Fonarow, 2020).

Epidemiological Profile and National Burden in India

The rapid and complete transition of the disease profile in India from communicable to non-communicable diseases has placed heart failure (HF) among the top public health issues in the country (Huffman & Prabhakaran, 2010). Indian patients, on average, are around 59 years old when they first develop heart failure (HF), which is considerably younger than those in the West, where the disorder is mostly diagnosed in the seventh or eighth decade of life (Harikrishnan et al., 2020; Sathish et al., 2024). The change is largely due to the "double burden" of modern drivers such as ischemic heart disease (IHD), hypertension, diabetes mellitus, and obesity, along with the continuation of more traditional causes like rheumatic heart disease (RHD), endomyocardial fibrosis, and pericardial disease related to tuberculosis (Huffman & Prabhakaran, 2010; Sathish et al., 2024).

In India, the number of people living with heart failure is estimated to have doubled over the last two decades. In the first half of the 2010s, hypothetical modelling works had put the number of HF patients in India between 1.3 and 4.6 million. Besides, the annual occurrence of HF was predicted to be between 0.5 and 1.8 million (Huffman & Prabhakaran, 2010). Today, the projections based on the registries and the trend are that the prevalence will go on increasing, crossing the 6 million marks before 2025 (Sathish et al., 2024; Shrivastava et al., 2024). More people have been getting chronic heart failure due to the rise in prevalence. The increase is attributed to the heightened occurrence of cardiovascular risk factors and the better survival after acute coronary syndromes (Sathish et al., 2024).

About 75% of HF cases in India are due to ischemic heart disease, figures from the National Heart Failure Registry (NHFR, 2019) illustrate (Sathish et al., 2024). Along with these, RHD and dilated cardiomyopathy are the main contributors; their incidences are declining, but they continue to dominate the younger age group and people from the less developed areas of the country (Huffman & Prabhakaran, 2010; Shrivastava et al., 2024). Besides, the outcome is still not satisfactory: the leading causes of death among Indian HF patients are pump failure and sudden cardiac death, with a one-year mortality rate of 21-27% being the range depending on the aetiology (Harikrishnan et al., 2020; Sathish et al., 2024).

The delay in the diagnosis, the limited accessibility of medical treatment according to the pre-set guidelines, and the financial obstacles to care, are systemic issues, which lead to the exacerbation of the overall burden of heart failure in India (Huffman & Prabhakaran, 2010; Sathish et al., 2024). The high impact on cardiovascular death over time is still the main characteristic of Heart Failure (HF), however the disease also represents a large socio-economic burden to the society due to frequent hospitalizations and loss of productivity in the younger, working-age population (Cook et al., 2014; Harikrishnan et al., 2020).

Pathophysiological Mechanisms and Etiology

The progression of heart failure is a complex multi-step that involves changes in both the anatomy and the function

of the heart, along with various other pathophysiological conditions (Katz, 1992; Mann, 2002). Myocardial infarction is responsible for one-third or more of cases of heart failure, as the infarction usually leads to fibrosis and the subsequent failure of the heart. Heart failure is mostly caused by coronary artery disease (CAD) (Heidenreich et al., 2022). The decrease of cardiac output as a result of tissue damage starts a process of neurohumoral activation, thus the vicious cycle is set in motion (Katz, 1992; Triposkiadis et al., 2023). With the activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS), the heart responds to the low blood flow situation with increased heart rate, vasoconstriction, and fluid retention Accordingly (Cohn, 2004; Katz, 1992). In general, these reactions that involve keeping blood pressure within normal range, have negative long-lasting effects that may become life-threatening in the end (Katz, 1992; Pitt et al., 1999).

The continuous increase in preload (the volume of blood in the ventricles) and afterload (the resistance the heart must pump against) causes chronic stress over the heart. Heart (ventricular) dilatation and hypertrophy follow from this structural remodeling, which further reduces one of the heart's major functions, i.e. pumping blood effectively (Lopez et al., 2017). Whatever might be the two aetiologies that start this cascade in question, there is no doubt that valvular heart disease, turning that already tough heart to a harder one due to malfunctioning valves and hypertension, making the heart endure chronic load pressure, are at least the two paths leading to this process as shown in figure 4 (Heidenreich et al., 2022).

Heart failure is a chronic condition which is mainly caused by neurohumoral activation and mechanical stress (Katz, 1992; Triposkiadis et al., 2023). These forces make the heart undergo significant changes in proteins such as progressing myocardial fibrosis, disturbance of calcium storage, and contractile protein loss (Lopez et al., 2017; Mann, 2002). As a result, heart muscle failure with decreased ejection fraction (HFrEF), i.e. loss of heart's pumping function, or heart failure with preserved ejection fraction (HFpEF), i.e. failure of the heart's relaxation/filling capacity, are the two clinical spectrum of this advancing failure (Lopez et al., 2017; Shah & Vaduganathan, 2010). Recognizing the interactions among these factors might provide us with better ways of prevention and treatment since they are considered as complex interrelations rather than separate functions.

MATERIALS AND METHODS

Multi-Omics Integration in Heart Failure

The classification of the heart failure solely on the ejection fraction basis, which was the first and is still the most common one, is beneficial in many respects. However, it does not represent the underlying molecular diversity of the disease (Shah & Vaduganathan, 2016; He et al., 2023). This variety is the source of the differing combinations of clinical results, which include treatment response and disease progression, among the patients that outwardly look the same. The development of high-throughput technologies has changed the situation radically, providing an exceptional opportunity to solve this puzzle by generating huge amounts of data from different molecular layers, or "omics." Nevertheless, the greatest achievement of this method is the bioinformatic rather than separate investigation of different layers. Multi-omics integration, which combines data from transcriptomics, proteomics, metabolomics, and genomes using advanced computational methods for the purpose of discovering underlying molecular mechanisms or endotypes of heart failure instead of mere clinical account, marks a revolutionary change in the paradigm (He et al., 2023; Red-Heart-Failure-Group, 2017).

Bioinformatic analysis is the first step in each omics layers. The genomic research such as Genome-Wide Association Study (GWAS) utilize statistical methods in order to uncover genetic variants that would be associated with cardiovascular diseases (Arnett et al., 2020). The functionally annotated variants are used to identify probable causative genes. Transcriptomics, which is mostly done by RNA sequencing, utilizes bioinformatic pipelines for the detection of differentially expressed genes and non-coding RNAs in failing and normal hearts (Red-Heart-Failure-Group, 2017). Pathway enrichment analysis points out the changed cellular processes that are relevant to the disease. Furthermore, transcriptomics is used to indicate changes in gene regulation, proteomics and metabolomics hold the keys for the functional output, and genetics rely on the evidence of susceptibility. As per the findings by He et al. (2023), the sum of these individual molecular layers only offers parallels of reality but does not yet suffice to delineate the whole picture. It is extremely important to combine bioinformatics layers. One of the ways to achieve this integration is network theory, machine learning techniques, and advanced statistical models (He et al., 2023; Rumsfeld & Curtis, 2019) are some of the methods used. Finding such a connection can unveil the "hub" nodes that are changed at multiple omics levels and thus the most highly ranked targets for therapy. The essence of the combination of these datasets is to uncover the complex chains of cause that link a genetic mutation to gene expression change, and hence protein network modification, and finally, a pathogenic metabolic shift becomes visible (He et al., 2023; Red-Heart-Failure-Group, 2017). In fact, the finding of novel, very different patient subgroups which are not segregated by ejection fraction but have common molecular profiles can be accomplished through the employment of unsupervised machine learning methods such as clustering on integrated multi-omics data from large patient cohorts (He et al., 2023; Shah & Vaduganathan, 2019). These biological endotypes

which are the most likely to be the basis of precision medicine, that is the treatment which is customized according to the unique biological signature of each patient, can also predict prognosis and more importantly, responses to certain drugs (He et al., 2023; Shah & Vaduganathan, 2016).

Single-cell omics technologies have revolutionized the landscape of research (Pinta & Taylor, 2016). These innovative instruments not only identify the new cell subpopulations that have been hidden in the studies of the bulk tissue, for instance, the pro-inflammatory macrophage subtypes or the particular fibroblast activation states, by the revelation of the cellular composition of the heart, but also provide the information on how the different cells interact to the occurrence of the inflammation, fibrosis, and hypertrophy by the visualisation of their communication networks using bioinformatics (Triposkiadis et al., 2023). Through their comprehensive profiling of the cell types of the myocardium, the authors' have paved the way for the novel, precise single cell targeted therapies. Furthermore, this study not only deepens the complexity of the multi-omics setting but also changes our understanding of cardiac tissue during the stress response and offers a little understanding of the progression of the disease for these new cell therapies.

Network Pharmacology of Phytochemicals

Indeed, some evidences have been provided to support the use of phytochemical-based therapy in the treatment of heart failure; nevertheless, misunderstanding of the mechanism of natural compounds is still widespread practice (Hopkins, 2007; Zhang et al., 2018). This is because phytochemicals are usually complex substances that interact with multiple targets instead of modulating one pathway only. Yet their multiple targets and complicated interactions allow them to be used for the complex pathophysiology of heart failure that derives from protein and pathway network malfunction. Network pharmacology, a systems-level approach to the polypharmacology of natural substances, is the main bioinformatics solution for this problem (Hopkins, 2007; Yildirim et al., 2011). One of the main advantages of the "network target, multi-component" approach is its conceptual similarity to the "one drug, one target" model, which has long been considered an obsolete idea. It is also consistent with the holistic view of traditional medicine and the complexity of the heart failure. Researchers can use computational tools to create and analyze the networks that link compounds and their interactions, thus allowing them to infer the likely overall disease network of different chemicals in plant extract (Ma et al., 2020; Zhang et al., 2018). This experiment can serve to test the hypotheses derived from such data concerning the possible therapeutic application of the substances.

By a stepwise bioinformatics method, network pharmacology is pragmatically implemented. The next step it performs is to look for the phytochemical active ingredients of natural drugs by first searching specialized databases like PubChem and the Traditional Chinese Medicine Systems Pharmacology (TCMSP) database (Ma et al., 2020; Zhang et al., 2018). The following significant step is forming hypotheses about the proteins that these substances target. This is done by using sophisticated algorithms in tools like SwissTargetPrediction and PharmMapper which assess chemical structures for possible binding sites (Ma et al., 2020). Simultaneously, a complete "heart failure disease network" is put together by integrating the genes and proteins related to HF that are identified from disease databases like OMIM and DisGeNET (Ma et al., 2020). The mapping of phytochemical targets on the HF network enables bioinformatic methods to locate these important overlapping nodes. The joining of these two networks allows the detection of central "hub" targets - proteins that are closely interconnected in the HF network and influenced by the phytochemical - thus, the integration made this discovery possible and these targets are most likely going to be very important in the treatment (Hopkins, 2007; Yildirim et al., 2011). By applying resources such as DAVID or KEGG, the technique of enrichment analysis is utilised to detect the affected biological pathways (such as neurohormonal activation, oxidative stress, apoptosis, and fibrosis) that relate to those common targets (Ma et al., 2020). Consequently, potential synergistic effects between the various compounds in the plant are also unveiled by providing a deep mechanistic indication of the plant's pharmacological action (Hopkins, 2007; Zhang et al., 2018).

Network pharmacology opens the door for the discovery of phytochemical candidates beyond luck and into the realm of rational drug discovery and drug repurposing by implementing this strong computational technique (Hopkins, 2007; Zhang et al., 2018). Multi-component substances can induce synergistic effects by this convincing systems-level explanation for the traditional medicines' mode of action which entails that such substances may target not only numerous proteins within a single coordinated pathway but also across multiple connected disease pathways. By not only substantiating the historical uses, this framework additionally infers the phytochemical's present-day application by recommending what combinations are most effective, which patients (based on their molecular endotype) may benefit the most and how natural compounds can be used in conjunction with synthetic drugs to make the therapeutic strategy more comprehensive (Ma et al., 2020). Therefore, network pharmacology is that crucial bioinformatic link connecting the front-end concepts of modern systems biology and personalized treatment for heart failure with the ancient knowledge of herbal medicine.

Molecular Docking of Phytochemical–Target Interactions

In order to figure out the binding mechanism more precisely, network pharmacology's prediction-which finds potential phytochemical-target interactions at the systems level-must be confirmed at the atomic level. Structural bioinformatics as the backbone computational method has a usage in this case

– that is molecular docking (Ferreira et al., 2022; Morris et al., 1998). The method of molecular docking introduces the most desirable position or 'pose' of a small molecule when the ligand like a phytochemical is combined with a target macromolecule e.g. a protein a rest for the pathophysiology of heart failure. The main aim is to estimate the binding affinity, i.e. the interaction's strength, which is an essential virtual screening criterion for lead compounds selection from the extensive natural products library, before spending money and time in lab test (Ferreira et al., 2022; Morris et al., 1998). In order to turn the multi-target predictions of network pharmacology into testable hypotheses and easily identify the most promising candidates for further research, the scientists can perform these interactions in silico.

The complete process of docking is a complex computational workflow. The 3D structure of the target protein, which is usually taken from databases like the Protein Data Bank (PDB), is generated by removing water molecules, adding hydrogen atoms, and locating potential binding sites (Ferreira et al., 2022). The 3D structure of the phytochemical is also made, and it is energy efficient. The docking algorithm then performs a conformational search which represents the millions of ways the ligand might be inserted into the binding pocket of the protein (Morris et al., 1998). A scoring function, which is a mathematical method that evaluates the binding free energy (ΔG, sometimes given in kcal/mol) is applied to each hypothetical position (Ferreira et al., 2022; Morris et al., 1998).One of the best ways to use molecular docking in the drug discovery process of heart failure drugs is by the implantation. It implies causality through tangible physical binding that is more credible than the simple correlation offered by network analysis. For instance, the best docking of resveratrol with SIRT1 gives a molecular rationale for its well-known cardioprotective effects, maybe through the activation of the pathways involved in stress tolerance and cellular energy metabolism (Howitz et al., 2003). Besides, docking also allows the comparison with the already existing traditional medicine; if, for example, a phytochemical such as curcumin shows a binding affinity similar to that of a known synthetic inhibitor for a particular inflammatory target then it indicates that curcumin might be a therapeutic agent (Liu et al., 2015; Shishodia & Aggarwal, 2004). However, it is still necessary to point out the limitations of the method. The accuracy of the docking result depends highly on the protein structure quality and the scoring function, which can be not very good in accounting for solvation effects and protein flexibility. So, the best way to look at molecular docking is as a very efficient hypothesis-generating and filtering tool rather than a final proof of activity (Ferreira et al., 2022; Morris et al., 1998). This method works well to select the top multi-target phytochemicals that have been revealed by network pharmacology, thus allowing a quicker transition of the ancient herbal-based treatments to scientifically validated drugs.

AI and ML-Powered Care Transformation

The predictive, data-driven domain of science, where AI and ML are the natural follow-ups to bioinformatics and thus are changing the whole research process of heart failure to a great extent (Rumsfeld & Curtis, 2019; Zhang et al., 2020). Managing and processing biological data of enormous scale is the main goal of traditional bioinformatics, yet AI and ML algorithms have the added capability to derive insights from this data, uncover complex, non-linear patterns and generate prediction models that are of a record-breaking accuracy. Due to the continued problems of heart failure such as the pronounced heterogeneity, the unpredictable progression, and the large proportion of novel therapeutic compounds that end up in clinical trials with no positive results, a change of strategy is required (Choi et al., 2018; Shah & Vaduganathan, 2019). By no means just a stage of better diagnosis and prognosis, the extensive adoption of AI and ML is prompting a transformation in the whole drug discovery process that is leading to the next era of proactive, personalized and preventive precision medicine in the treatment of heart failure (Rumsfeld & Curtis, 2019; Zhang et al., 2020).

Successful cases of AI application in healthcare management have already been gathered. Several machine learning models, in particular supervised ones (e.g. Random Forest, Support Vector Machines, and Neural Networks), are being trained on large-scale Electronic Health Records (EHR). Clinical factors, laboratory results, imaging reports, and increasingly omics data are the major components of these databases. Most of the times these models have a higher performance than traditional risk scores when they are used to predict the risks of hospitalisation, death, or sudden cardiac death of a patient (Choi et al., 2018). Moreover, unsupervised learning methods such as clustering are applied in a,data-driven phenotyping that might lead to more personalized treatment by identifying different subgroups of heart failure patients with similar clinical and molecular data patterns (Shah & Vaduganathan, 2019). Machine learning and deep learning have gone a long way in medical imaging, where the former is limited by the availability of only structured data. One of the ways of achieving this is by spotting the very small patterns in cardiac MRIs and echocardiograms that people can hardly see, by estimating the occurrence of anomalies of wall motion, and by accurately and automatically measuring the ejection fraction (O'Connell et al., 2022). These are the grounds for both standardization of diagnostics and the reduction of inter-observer variability.

AI is drastically accelerating the cleaner and the better identification of novel therapies, for instance, phytochemicals, in the domain of discovery (Zhang et al., 2020). Using a machine learning algorithm, several virtual compounds, among them those from natural product libraries, are inspected for those that may potentially bind tightly to the

most essential HF targets depending on the known structure and biological activity of the compounds. Compared to traditional high-throughput methods, the in-silico screening process is incredibly fast and cost-effective. Moreover, there is also the use of generative AI, which might be inspired by the architectures of the successful phytochemicals in producing completely new molecular structures with the right multi-target profiles for heart failure. In order to be used for a specific purpose, these synthetic intelligence-generated compounds can be designed to have certain characteristics such as high effectiveness, minimal toxicity, and good bioavailability (Zhang et al., 2020). Besides fueling the scientific research on heart failure using such robust computational tools, AI and ML are also revolutionizing the entire industry by providing researchers a potential approach to unravelling the complexity, predicting its progression, and creating the smartest forthcoming therapies.

RESULTS AND DISCUSSION

Pharmacological Foundations for Therapeutic Approaches and Plant-Based Mechanisms

The "four pillars" of treatment, encompassing beta-blockers, sodium-glucose cotransporter-2 inhibitors (SGLT2is), mineralocorticoid receptor antagonists (MRAs), and angiotensin receptor-neprilysin inhibitors (ARNIs), have largely changed the pharmacological management of heart failure (HF) gradually through several years (Heidenreich et al., 2022; Yancy et al., 2013). The main factor leading to the broad implementation and spread of these therapeutic agents was their winning effectiveness, which was the essence of landmark clinical trials that demonstrated a consistent decrease in both morbidity and mortality.

Beta-blockers- One of the first medications to demonstrate a notable reduction in mortality was beta-blockers. The drugs have been shown to lower hospitalizations and deaths, as they minimize the harmful impact of the sympathetic nervous system, which is the main cause of the adverse effects (Heidenreich et al., 2022; Yancy et al., 2013). In this way, they eliminate the risk by lowering heart rate, blood pressure, and combating the negative effects of prolonged adrenaline exposure on the heart (Triposkiadis et al., 2023).

Mineralocorticoid Receptor Antagonists (MRAs)- Mineralocorticoid receptor antagonists (MRAs) including eplerenone and spironolactone have been demonstrated via clinical trials like RALES to stop the occurrence of the harmful effects of aldosterone (Pitt et al., 1999). Aldosterone, a hormone that regulates fluid balance in the body, may lead to cardiac fibrosis and arteriosclerosis. MRAs suppress the receptor, hence they enhance cardiac performance and lower the chances of rehospitalization (Pitt et al., 1999).

Angiotensin Receptor-Neprilysin Inhibitors (ARNIs)- The introduction of sacubitril/valsartan, an Angiotensin Receptor-Neprilysin Inhibitor (ARNI), marked a significant breakthrough during the neurohormonal era. It was established that ARNI, compared with a standard ACE inhibitor, had a very substantial effect in minimizing heart failure hospitalizations as well as cardiovascular deaths in the landmark PARADIGM-HF trial (McMurray et al., 2014). ARNI derives its power from its combined mode of action—inhibiting the neprilysin enzyme, which stops the degradation of the vital natriuretic peptides that lower blood pressure and fluid retention, and at the same time, occluding the angiotensin II receptor (like an ARB) (McMurray et al., 2014).

Sodium-Glucose Cotransporter-2 Inhibitors (SGLT2is)- For the first time, drugs SGLT2 inhibitors that later were shifted to diabetes treatment, have changed the whole treatment of heart failure (Packer et al., 2020). The main experiments like DAPA-HF and EMPEROR-Reduced showed that these medications cut cardiovascular death and hospitalization to a great extent, and this is so, no matter the patient being a diabetic or not (Packer et al., 2019; Packer et al., 2020). Besides easy glucose control, their multifaceted mechanism of action also involves diuretic effect, better cardiac metabolism, and a decrement in inflammation and fibrosis as shown in figure 5 (Packer et al., 2020).

The use of sodium-glucose cotransporter-2 inhibitors (SGLT2is), initially planned for diabetics, has changed dramatically the therapy of heart failure (Packer et al., 2020). The main trials, DAPA-HF and EMPEROR-Reduced, indicated that these drugs result in a substantial decrease in the combined endpoint of cardiovascular death/prolonged hospitalization, on both patients with diabetes and patients without diabetes (Packer et al., 2019; Packer et al., 2020). Besides blood glucose control via different pathways, the drugs also empower the patient's metabolism; they may lower inflammation and treat fibrosis as well (Packer et al., 2020).

The discovery is very useful in medical treatment. As a result of these findings, changes in the clinical guidelines that are implemented globally have occurred, and these four pillars are now considered the basis of treatment for almost all the HFrEF patients (Heidenreich et al, 2022; Yancy et al., 2013). Moreover, the transition of SGLT2is from HFpEF and HFmrEF to the situation of ejection fraction has led to the evolution of therapy for nearly all HF patients with a mortality-reducing, evidence-based regimen (Anker et al., 2021; Heidenreich et al., 2022). The use of a neurohormonal-targeted therapy combination is essential, and this holistic approach constitutes a new era of timely and efficient HF management.

Flavonoids and polyphenols are the most talked-about substances, among several chemical classes, that confer the cardio protective effects of natural products. Besides the direct effect on the main pathophysiological mechanisms

of HF, these compounds also provide the body with several pharmacological features as shown in figure 6. (Sun et al., 2017).

Resveratrol: Resveratrol is one of the polyphenols that occur naturally in peanuts, berries, and red grapes. The hallmark of resveratrol is the activation of the sirtuin enzymes, especially SIRT1, which is one of the proteins linked to prolonged life and higher resistance to cell stress (Baur et al., 2006; Howitz et al., 2003). Besides that, resveratrol can bring back mitochondrial function and induce a better metabolic profile of the cardiac cells in the event of heart failure (Baur et al., 2006).

Quercetin: Quercetin, one of the most powerful antioxidants, is found in onions, apples, and black tea. Along with that, quercetin can reduce oxidative stress, which is the primary source of heart diseases, and eliminate free radicals (Sun et al., 2017). Besides this, the suppression of enzyme activity has been confirmed to reduce the chronic inflammation phase in cardiac remodeling (Mann, 2002).

Curcumin: Curcumin is the most important ingredient in turmeric which is a polyphenol with powerful anti-inflammatory and antioxidative properties (Liu et al., 2015; Shishodia & Aggarwal, 2004). Its thwart inflammation mechanisms such as NF-κB, an agent that may lead to the overexpression of genes which by virtue of cardiac fibrosis and hypertrophy are promotive (Liu et al., 2015; Shishodia & Aggarwal, 2004).

The phytochemicals are non-single-action, multi-target cardioprotective agents.

Anti-inflammatory Properties: Simple persistent inflammation leads to heart insufficiency (Mann, 2002). The polyphenol flavonoids quercetin and curcumin that change the inflammatory signal pathways, can diminish an array of pro-inflammatory cytokines among which TNF-α and IL-6 (Liu et al., 2015; Shishodia & Aggarwal, 2004).

Antioxidant Properties: Over time, the oxidative stress that results from the imbalance between free radicals and the body's antioxidant protection system can cause cell damage that is irreversible (Sun et al., 2017). Flavonoids and polyphenols which are strong antioxidants neutralize these dangerous chemicals, and they protect cardiomyocytes from damage (Sun et al., 2017).

Anti-fibrotic Properties: Cardiac fibrosis is a condition in which the heart becomes stiff and loses its efficiency due to the excessive production of fibrous connective tissue (Lopez et al., 2017). The research shows that substances such as curcumin and resveratrol could contribute to the prevention of cardiac fibroblasts proliferation and fibrosis signaling pathways, thus, helping the heart to maintain its natural softness (Liu et al., 2015).

Molecular Docking Analysis of Cardioprotective Phytochemicals

The more negative the binding energy, the higher the connection is stronger and thus more likely to have a biological activity, a principle demonstrated in the docking studies of natural compounds like those in Huangqi Fuling decoction (Luo et al., 2025). For that specific target, researchers would select quercetin first as it can be seen from Table 1 that it has a binding energy of –10.2 kcal/mol for MAPK which is a better binder than curcumin that has a binding energy of –9.2 kcal/mol for NF-κB. Besides, the result allows a visualization of the fundamental molecular interactions that keep the complex stable, for example, ionic bridges, van der Waals forces, hydrogen bonds, and hydrophobic contacts. One example of such atomic characteristics is 8-Prenylgenistein's activation of AMPK (Arulkumar et al., 2024) which essentially outlines the mechanism of inhibition or activation and also helps to identify the future changes that would be logical to the natural scaffolds for their improved activity and selectivity as shown in figure 7.

Proteins associated with heart failure have been targeted through molecular docking using three phytochemicals: quercetin, resveratrol, and curcumin. The present findings highlight binding energies, key interactions, and relevant citations among the various pharmacological potentials of curcumin and its derivatives (Chen et al., 2024).

CONCLUSION

Heart failure (HF) is among the major and growing worldwide health problems, that have been caused, in large part, by the aging of the population and the increase in diseases such as diabetes and hypertension. Initially, it was considered to be just a pump failure, however, now it is recognized as a complex neurohormonal disease, hence life-saving medications such as SGLT2 inhibitors, beta-blockers, ARNIs, and MRAs have been created. Among other reasons, patient diversity in treatment response and disease progression still remains a challenge which has lead to the search for new remedies. Precision medicine is allowing more detailed molecular subtyping and more rational drug repurposing with the aid of the advanced techniques of network pharmacology, multi-omics integration and artificial intelligence. The list of natural substances which can protect the body from different kinds of damage is led by resveratrol and curcumin. The breakthrough in the field of medicine was the extensive use of machine learning and molecular docking for the targeted creation and validation of new drugs. These transformations, overall, have a great opportunity to revolutionize patient outcomes in numerous populations across the globe simply by moving away from the standard therapeutic approaches and going towards personalised, preventive, and predictive heart failure treatment.

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Table 1: Binding affinities and molecular interactions of phytochemicals with heart failure-related protein targets determined by molecular docking analysis.

Phytochemicals	Target Protein	Binding-Energy (kcal/mol)	Key-Molecular Interactions
Quercetin	NF-κB	-9.2	Hydrogen bonds with ARG-225, THR-148
Resveratrol	SIRT1	-8.5	Hydrophobic interactions with LEU-133
Curcumin	MAPK	-10.2	Multiple hydrogen bonds in the active site

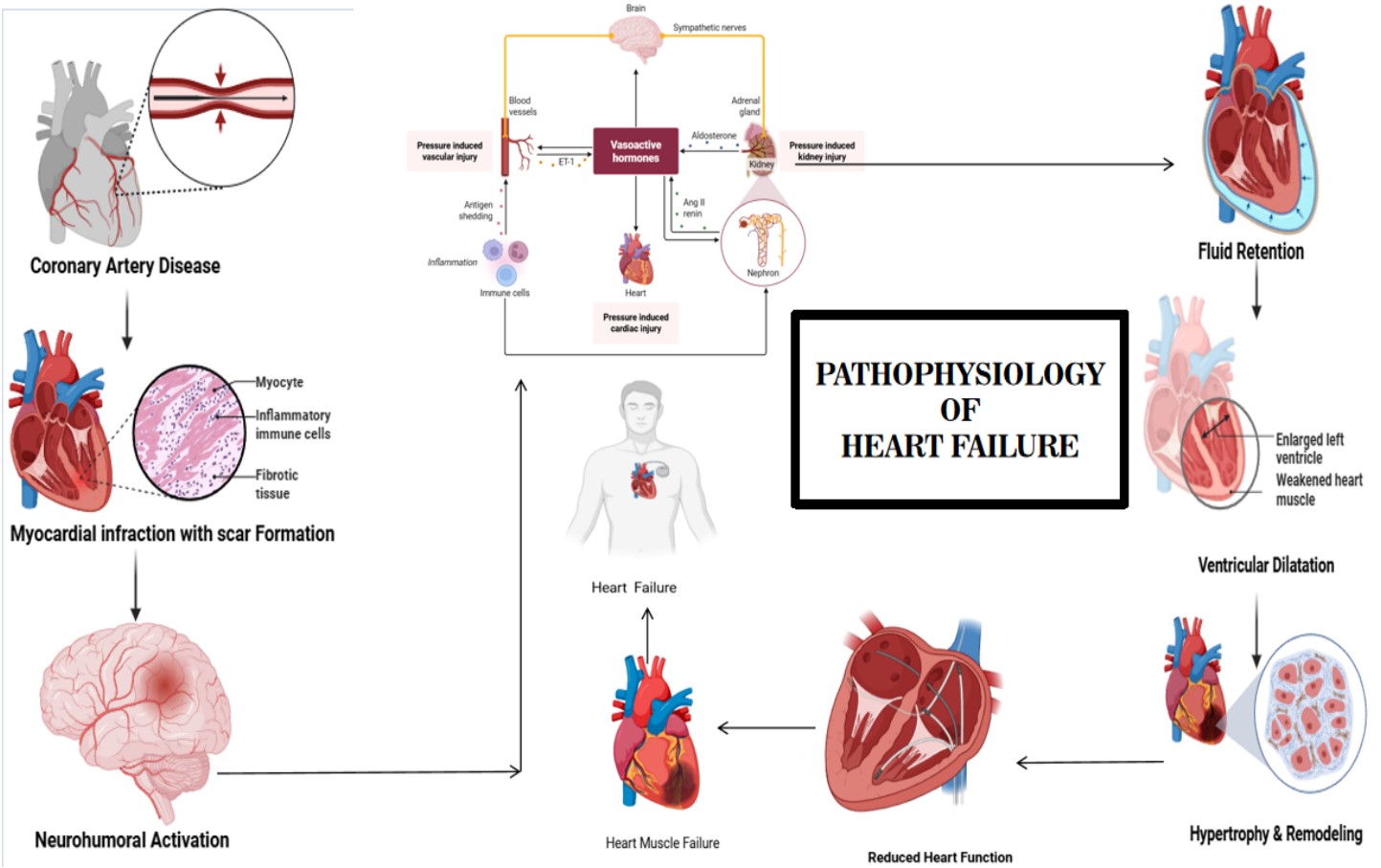


Fig. 1: Heart failure usually results from an original heart damage, for example, a myocardial infarction, after which the scar tissue develops and the heart performance is lowered. The scar tissue causes the body to activate the neurohumoral system, which delivers more hormones that not only worsen the heart, but the blood vessels and kidneys as well. The organs malfunction signs are fluid retention, ventricular dilation, and remodeling of the heart muscle. Eventually, the clinical heart failure symptoms develop as the heart has lost most of its capacity to pump effectively.

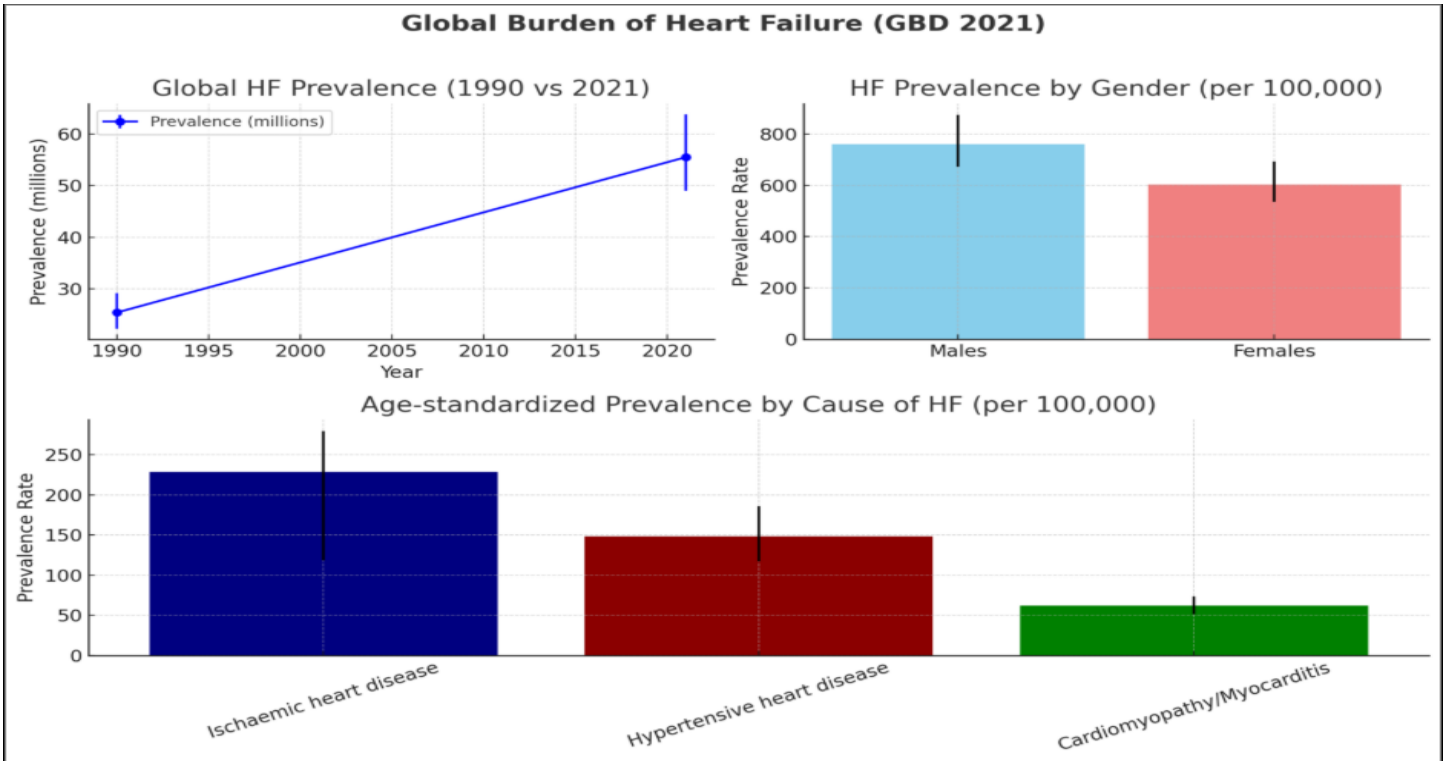


Fig. 2: Global heart failure (HF) burden trends, GBD 2021 estimates. Top: HF prevalence by gender and worldwide prevalence from 1990–2021. Bottom: HF age-standardized prevalence (per 100,000) per underlying aetiology.

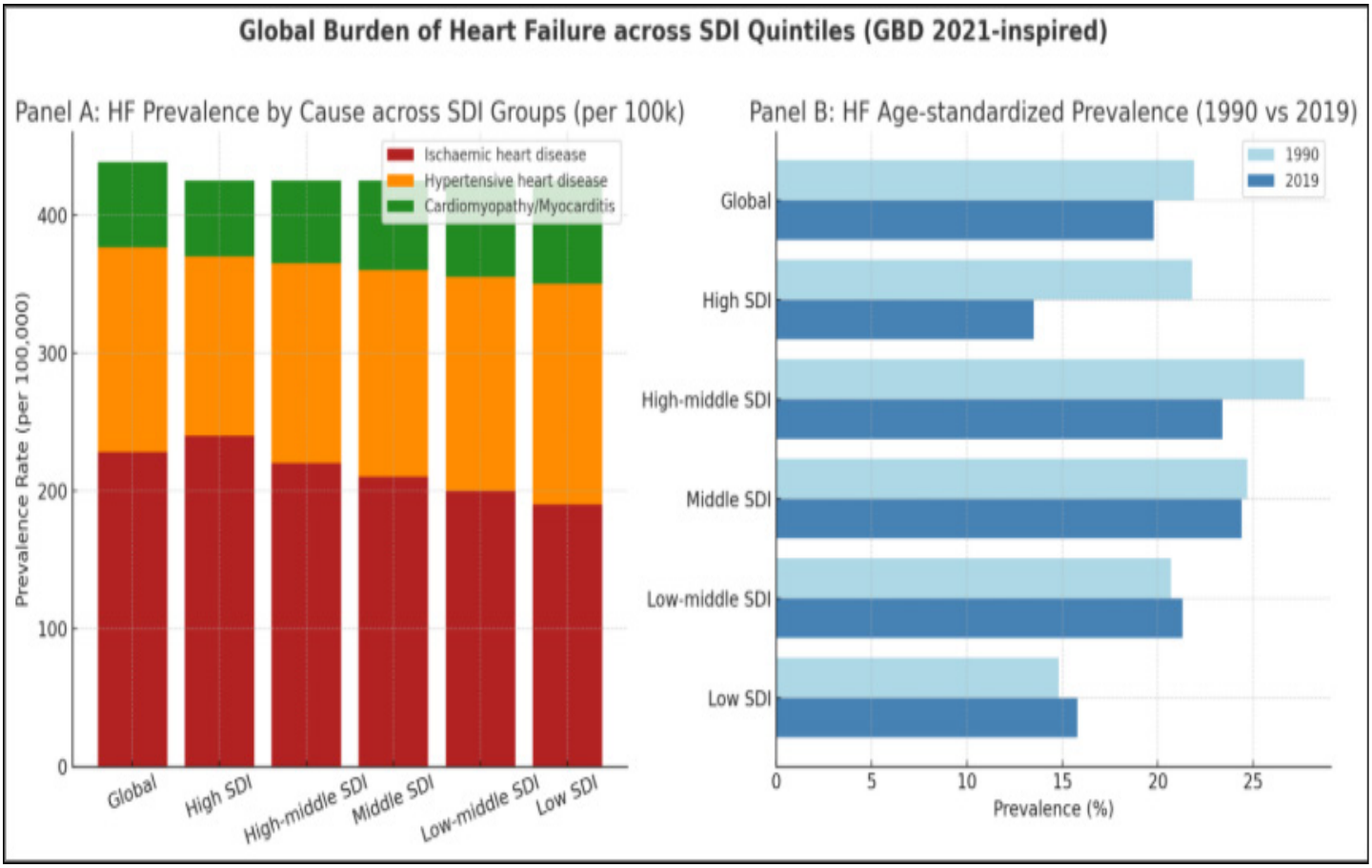


Fig. 3: Heart failure (HF) incidence depending on SDI quintiles all over the globe. Panel A visualizes the breakdown of HF prevalence due to different causes (ischaemic, hypertension, cardiomyopathy/myocarditis). Panel B illustrates the age-adjusted prevalence of HF in the various SDI classes in 1990 and 2019.

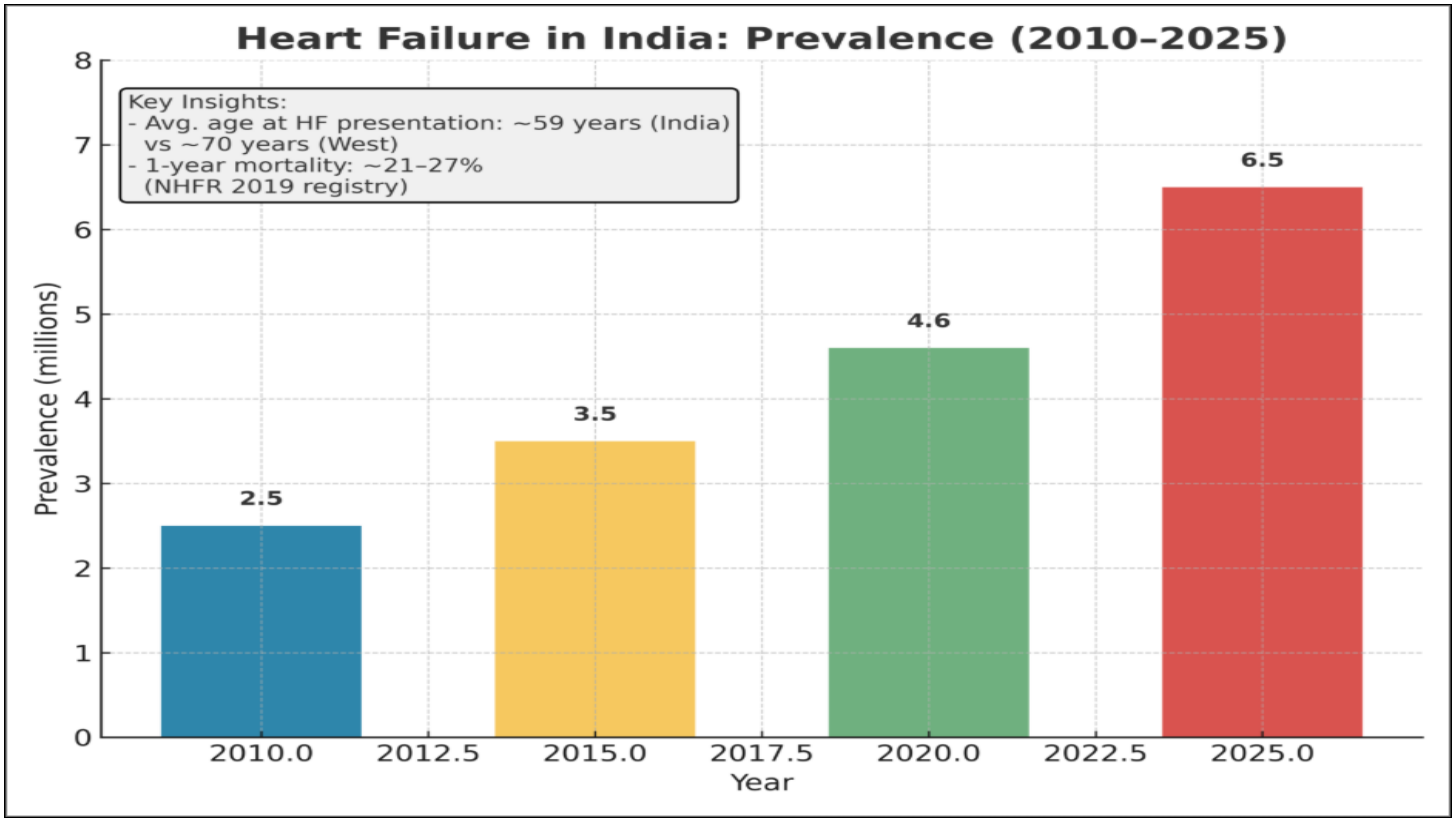


Fig. 4: Depicts the increasing prevalence of HF in India from 2010 to 2025, showing the extent of the problem and the urgent requirement of both health system readiness and preventive actions.

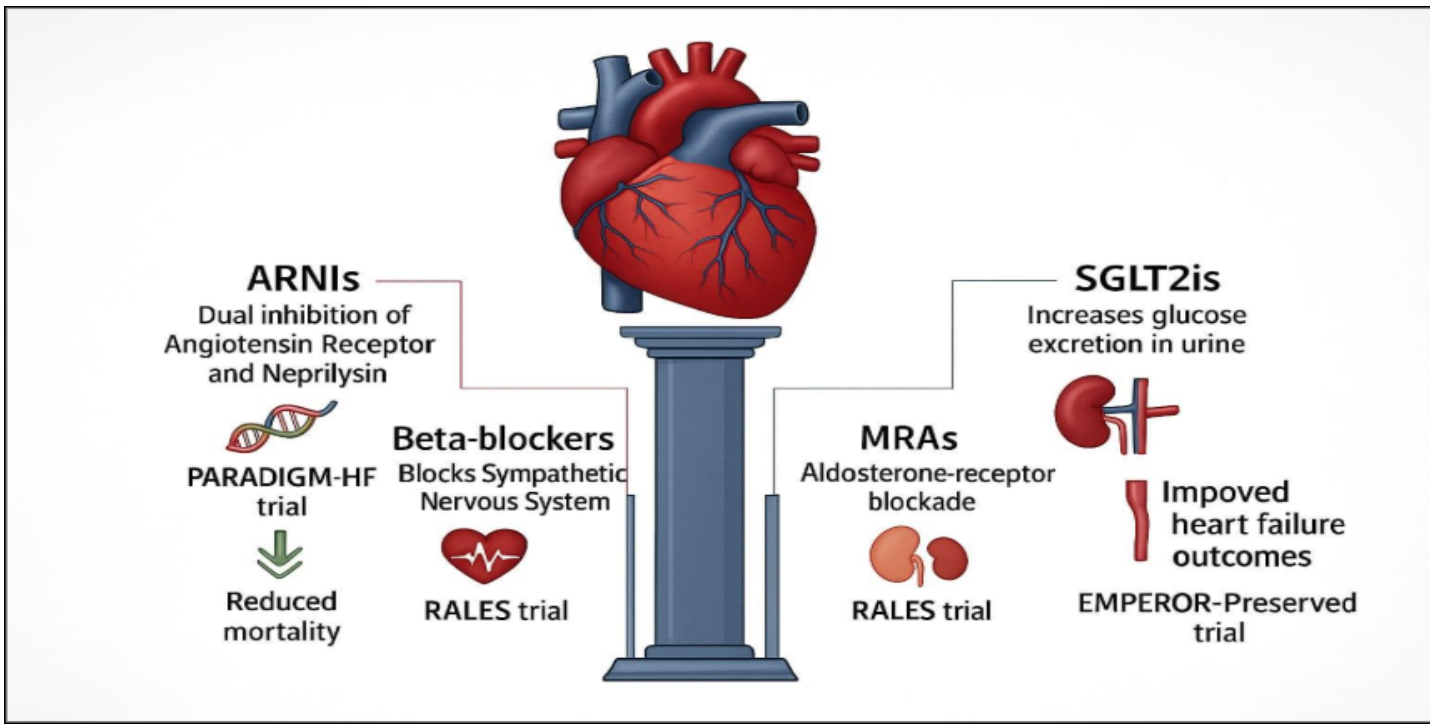


Fig. 5: Major drug classes in the treatment of heart failure. The therapies nowadays in heart failure comprise the medications of four classes: Angiotensin receptor–neprilysin inhibitors (ARNIs), beta-blockers, mineralocorticoid receptor antagonists (MRAs), and sodium-glucose co-transporter-2 inhibitors (SGLT2is). The use of all these drugs is based on the evidence from the clinical trials (PARADIGM-HF, MERIT-HF, RALES, EMPEROR-Preserved) linking the administration of these classes to such benefits as lower mortality, reduced hospitalizations and improved outcomes.

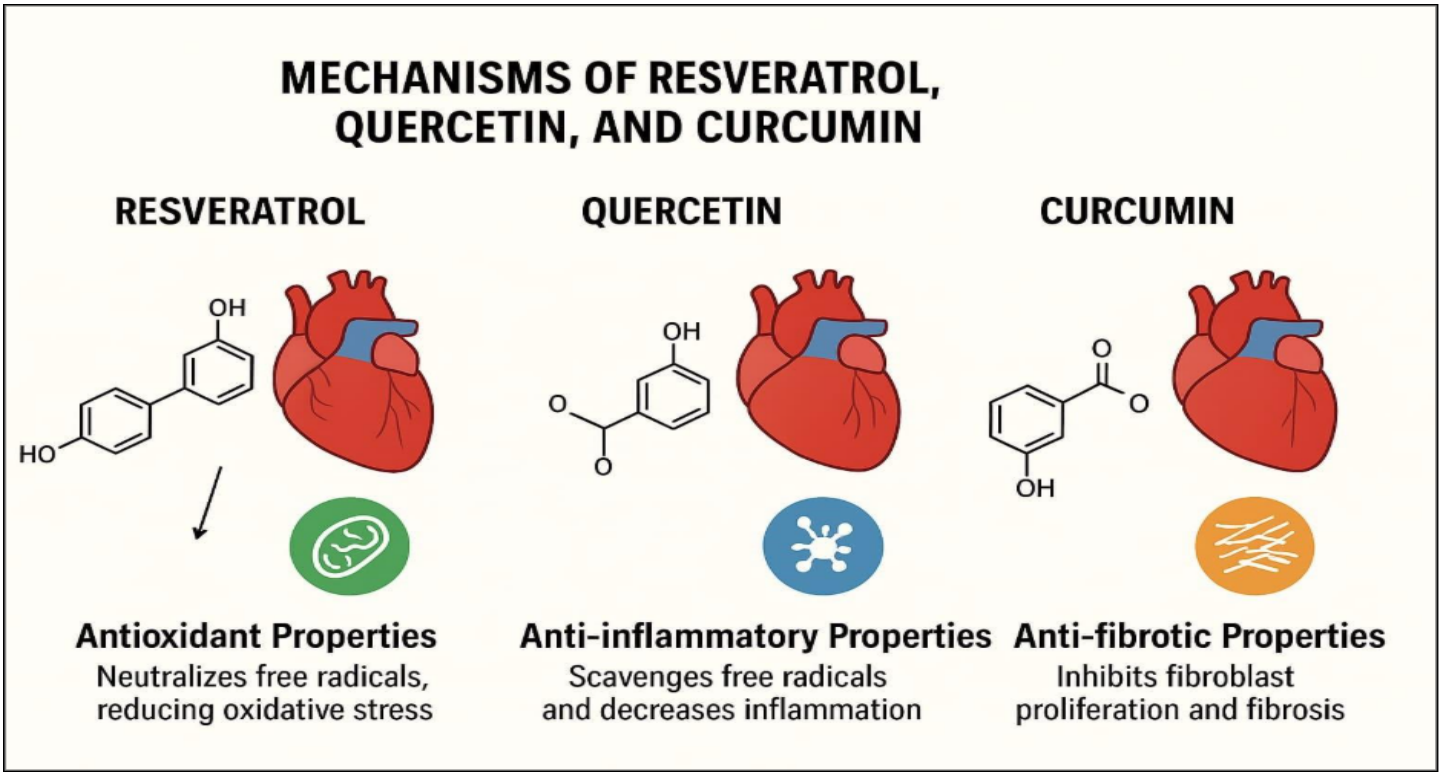
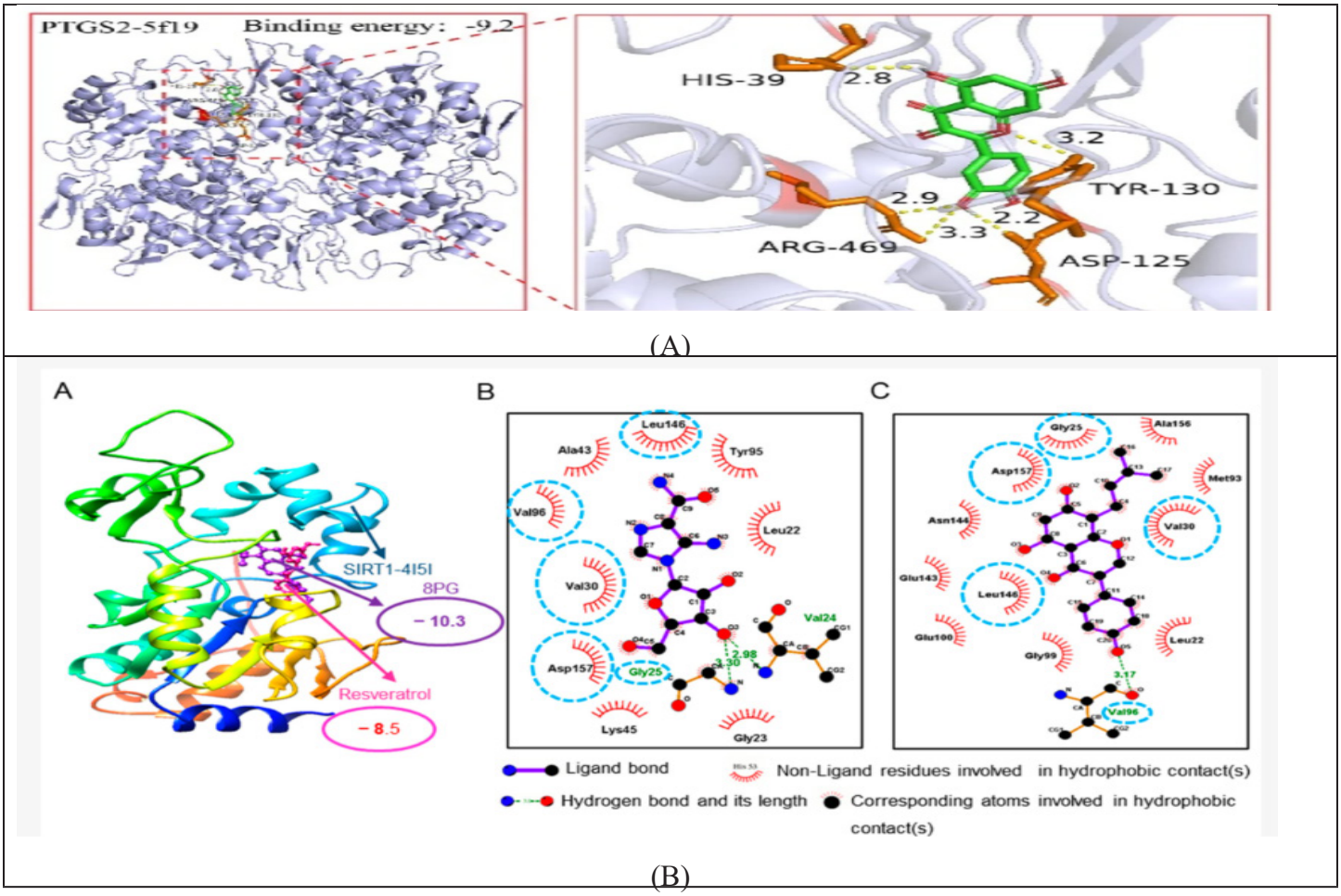
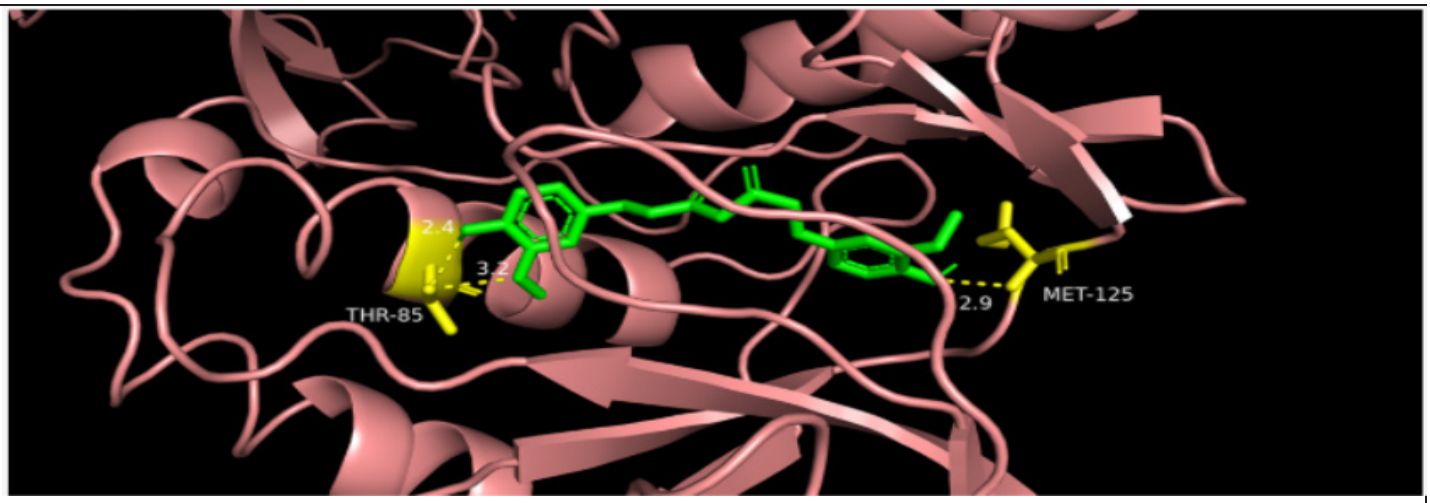


Fig. 6: The mechanisms of cardio protection of major phytochemicals. Quercetin (apple, onion) eliminates free radicals and reduces oxidative stress; curcumin (turmeric) inhibits the inflammatory pathways and prevents fibrosis; and resveratrol (grapes) elevates mitochondrial function and keeps a good metabolic profile. These naturally occurring substances have multi-target cardioprotective effects, which are relevant to the therapy of heart failure.





(C)

Fig.7: Molecular docking of phytochemicals with heart failure–related target proteins. (A) Quercetin–PTGS2 complex shows –9.2 kcal/mol binding energy with H-bonds to ARG-225 and THR-148. (B) Resveratrol–SIRT1 exhibits –8.5 kcal/mol energy with hydrophobic interaction at LEU-133. (C) Curcumin–MAPK shows strong binding –10.2 kcal/mol with multiple hydrogen bonds.